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MINIREVIEW

Influenza Seasonality: Underlying Causes and Modeling Theories[▽]

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INFLUENZA SEASONALITY: VIROLOGICAL AND EPIDEMIOLOGICAL PERSPECTIVES

Influenza (or "flu") leads to the hospitalization of more than 200,000 people yearly and results in 36,000 deaths from flu or flu-related complications in the United States (15), striking both the elderly and infant populations particularly hard (24). Two members of the *Orthomyxoviridae* family, the influenza A and B viruses, are the primary causes of this acute viral respiratory disease. Both viruses are characterized as enveloped viruses that contain eight negative-stranded RNA segments that encode 9 structural and 2 nonstructural proteins (influenza A virus) or 10 structural and 1 nonstructural protein (influenza B virus). Because of the higher levels of morbidity and mortality associated with influenza A virus, in part due to the large reservoir of the virus in aquatic birds, we will restrict ourselves to discussions of this virus.

Each influenza A virus particle is surrounded by a host cell membrane, where two out of three surface proteins, hemagglutinin (HA) and neuraminidase (NA), are responsible for viral entry into the host cell and are the targets of B-cell immunity (13). While 15 subtypes of HA and 9 subtypes of NA exist in the wild, historically only HA subtypes 1, 2, and 3 and NA subtypes 1 and 2 have been responsible for stable human infections (49). Human variants of HA subtypes 1 to 3 have high affinity to NeuAα 2,6Gal-containing receptors on the mucosal lining of the human bronchopulmonary system and are responsible for viral binding to the potential host cell. NA's enzymatic cleaving of sialic acid appears to have functions both in reducing the number of "decoy" receptors that may render viruses attachment to epithelial cells of the bronchopulmonary system (56) and, critically, in allowing the release of viral particles from infected cells (4).

Two processes allow the virus to quickly change in response to selection and to adeptly evade B-cell immunity through neutralizing antibodies (immunoglobulins). One is "antigenic drift," the remarkable ability to mutate rapidly, a function of the infidelity of RNA polymerases. This mutation alters the major antigenic proteins, HA and NA, which can maintain their functions while undergoing considerable amino acid substitutions (12, 31). The mutation effect is more restricted for other proteins involved in viral RNA replication and packaging of the viral genomes. The second process, "antigenic shift," is the ability of the virus to undergo reassortment of its genome when more than one virus has infected a cell, a function of the segmented viral genome. Combination of these processes leads to viruses capable of evading host B-cell immune responses (20, 82). The pathogen originates in avian host species and is traditionally thought to infect human populations only via intermediary hosts (e.g., pigs), although there is now evidence that direct bird-human transmission is also possible (74).

Novel influenza virus strains can be the source of infrequent but devastating pandemics, most famously the 1918 pandemic, which killed between 20 and 40 million people (43). These pandemics are associated with major shifts in the HA and NA proteins that define viral strains. More routinely, influenza virus also generates epidemics or large outbreaks. Epidemics can be traced to a drift in the HA and NA proteins that circumvents sufficient preexisting B-cell reactivity so as to render the individual susceptible. Often the influenza virus may produce sporadic localized outbreaks. Such cases have not been the focus of research into influenza epidemiological virology, but it is likely that they are also associated with a transient viral subpopulation with immunoevasive properties, a theory which has been borne out with mathematical models (31, 68, 69).

In temperate climates, flu infections at whatever level of intensity are characterized by a flu season. In these areas, the disease is thought to exist at a low level throughout the year but exhibit a marked seasonal increase, typically during the winter months. Influenza epidemics and outbreaks occur in tropical areas as well, although the timing and impact are not as well defined (16, 71, 81). Local epidemics begin suddenly, peak in 2 to 3 weeks, and last for a total of 5 to 10 weeks. It is believed that in most cases seasonal outbreaks of influenza originate in China and spread from there (19).

Infectious disease dynamics offer a wide variety of intriguing and unexplained phenomena, yet none is as consistently observed while still remaining so poorly understood as the seasonality of influenza. There is a gap in how diverse studies encompassing immunology, mathematics, epidemiology, and virology combine to form a complete picture of flu seasonality. This may be due to the daunting complexity of seasonality itself, which is likely to reflect the actions of a vast multitude of variables. For whatever reason, only limited research has actually focused on supporting or rejecting each of the proposed underlying causes of the seasonality of influenza, and most of

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these, while thorough and well supported, are largely confined to a single discipline. This paper will provide a review of the proposed theories from the existing literature and examine possible links among them that may suggest a more-unified view of influenza seasonality, as well as call attention to gaps among the different ways of understanding seasonality. It may be that, once actually understood, the mechanisms governing the seasonal pattern in the incidence of influenza can provide greater insight into all aspects of the dynamics of transmission and maintenance of this disease (59). The authors believe that the current research has reached a stage such that advances in our understanding of influenza seasonality will emerge from an enhanced conceptual understanding of the biological dynamics of infection, not from a breakthrough in mathematical methodology. Therefore, the bulk of the review is devoted to the disease parameters being modeled rather than to modeling techniques, although these are briefly examined in their potential applications.

BIOLOGICAL CAUSES: SEASONALITY AS AN EMERGENT PROPERTY OF VIRAL INFECTION AND HOST STATUS

Viral evolution and the immune response to the virus. As described above, influenza A virus is extremely adept at both evading the host immune system and achieving heightened virulence. The HA and NA antigenic epitopes of influenza A virus have very high rates of mutation (estimated at 6.7×10^{-3} nucleotide substitutions per site per year for HA). When properly positioned, these mutations can prevent the immunoglobulins raised against the HA and NA from previously encountered strains from binding to the mutant (33, 45). This results in the rapid turnover of viral strains, hampering (though not totally negating) the abilities of previously generated B-cell-mediated immune responses to guard against reinfection, even within the span of only a relatively few viral generations. Small, subtle mutations in HA and NA are incapable of escaping the limited cross-protection from closely related viral strains that the proliferation of B cells provides, preventing the diversity of circulating strains from increasing explosively (31). This gives influenza virus its characteristic epidemiological profile of a frequently shifting dominant subtype rather than a huge number of closely related subtypes, which often appear in other rapidly mutating RNA viruses (22). Models incorporating this limited cross-protection driven by viral adaptation and immune responses have been shown to generate cyclical patterns closely resembling the seasonal patterns observed with influenza virus infection (31).

Influenza B virus mutates at a much lower rate (3.2×10^{-3} nucleotide substitutions per site per year) (58), though under similar selective pressure, and appears to rely less on the dramatic genetic reassortment from which much of influenza A virus's variability is derived. While the complete mechanism of viral evolution of influenza B virus is not yet understood, this slower and more-erratic viral evolution may be the driving force behind both the less-frequent and the less-periodic emergence of influenza B virus capable of infecting large numbers of people (58). Because influenza B virus is restricted to its human host, the lack of an external reservoir in which the virus can evolve independently may also play an important role in its decreased virulence, although there is some suggestion that the virus may have a reservoir in seals (62).

While antibody-mediated protection is generally considered the primary protection against infection, another source of protection is mediated by CD8 T cells that kill already infected host cells. This cellular immunity does not protect against infection but can rapidly ameliorate infection. Immunological studies conducted on human populations revealed an interesting pattern, in which a T-cell-mediated immune response is targeted against most conserved influenza virus proteins, such as the matrix protein M1 and the nucleoprotein NP, which are important in viral-particle assembly and extrusion (budding). In fact, age-related studies concluded that, by the age of 15 years, children develop anti-influenza virus CD8 T-cell memory comparable with that of adults (48), and the frequencies of memory cells might reach 0.11 to 0.56% of the total CD8 T-cell pool (44). However, there is a report that memory T cells specific to influenza virus antigens, occurring at a high frequency among CD8 T cells in the peripheral blood, might have diminished functional capacities, such as production of interferon-g and antigen-induced proliferation in elderly individuals, hampering their abilities to control the magnitude of viral infections (23).

The role of CD4 T cells in the immune response to influenza virus is well described (14, 65, 72). Mature B-cell responses generally require T-cell help; thus, a viral antigen must be able to both stimulate the B cell (hapten) and provide a T-cell epitope (carrier). While it is possible that very mature B memory cells may be able to dispense with T-cell help, for most responses the absence of T-cell help could lead to an absence of B-cell effector function. CD4 T cells may also play a role in generating a strong CD8 memory response.

The cyclical patterns of other viral diseases with different immunological and virological behaviors can provide useful comparisons to those of influenza virus. Measles shows a clear cyclical epidemic pattern, although outbreaks are often separated by years rather than seasons (32, 55). However, in this disease, human immune memory provides a powerful, lifelong immunity subsequent to initial exposure. This limits the potential of a population to sustain epidemic levels of infection after an outbreak until the birth rate and immigration can once more provide a sufficiency of susceptible hosts. Influenza virus's ability to evade protective immunity via the introduction of new strains replenishes the pool of available susceptible hosts much more rapidly, shortening the expected length of the epidemic cycle (38). What is lacking is a linkage between viral evolution and the wide assortment of other potential factors in influenza seasonality. Theoretical modeling of viral evolution, or empirical studies, when combined with the examination of high-level weather events, mass population mixing, and other seasonality factors could establish whether viral evolution is a cause or an effect of differing pathogen-host relations and disease profiles and how these interact on a microbiological level, where vaccines and prophylactics can address the disease directly.

Seasonal host health. Seasonal variations in the health and physiological statuses of animals are quite common. It is not surprising that the immune system may experience a pattern of ebb and flow that could leave a host animal vulnerable to infection. It has been suggested that the observed seasonality of influenza is the result not of sweeping waves of disease traveling across

the globe but rather of a constant level of infection mediated differently by the host immune system over time. Specifically, it has been posited that light/dark cycles, manifesting as melatonin levels, may have an impact on the immune system, rendering the host more susceptible to infection at different times of the year by pathogens which are present year-round (25). While little direct evidence linking seasonality to susceptibility to influenza virus infection has yet been published, there is a strong case for the biological plausibility of such a relationship. For instance, photoperiod—a useful measure of seasonal variations in light exposure—has been shown to have an impact on the immunocompetence of Siberian hamsters and mice, raising certain immune responses and lowering others (83).

Two possible intermediaries between photoperiod and immunity are melatonin and vitamin D (25-hydroxy-vitamin D). Melatonin appears to work partly by regulating the host immune response via interleukin-1β (IL-1β) levels, which rise when melatonin is present and can exhibit a protective effect in some viral infections (10). Further studies with mice have shown that an IL-1β deficiency results in a higher mortality rate upon influenza virus infection (47). Vitamin D levels have a strong effect on immunity by promoting CD4 T-cell and mucosal antibody responses (41), and vitamin D levels are directly related to the amount of sunlight. In both these cases, photoperiod effects may be considered as altering normal levels of immunity. The relative impact of each—as well as other factors—is not yet quantified, however, and there is ample opportunity for further examination. Dowell (25) discusses several studies demonstrating that subjects exposed to influenza virus during the summer were less likely to develop the disease than those exposed in the winter, suggesting a host-based defense mechanism active at high levels during the summer. Left unexplored is the possibility of seasonal fluctuations in the nature of the virus itself. A clear and definitive relationship between photoperiod, host immune response, and influenza virus infection has yet to emerge, but the groundwork has been laid for continuing research.

Host nutrient intake may also contribute to the seasonal patterns of flu occurrence. Low host levels of selenium lead to an increase in the rate of viral mutations, particularly in the coding of the viral protein M1, which has been shown to increase virulence in mice (9, 60). Additionally, mice fed a long-term diet rich in the antioxidant vitamin E have been shown to have lower virus titers in the lungs after challenge with influenza virus as well as fewer of the anorexic symptoms of influenza virus infection that lead to weight loss (40). As both vitamins are taken up in food, it has been proposed that seasonal fluctuations in diet (due to the availability of certain foods) lead to a decrease in antioxidant levels, an increase in oxidative stress, and a commensurate increase in viral mutation and, therefore, infection rates. The solid and well-supported biological plausibility of the host's physiological standing contrasts with a paucity of epidemiological evidence for the same. Questions of how largely local variations in immune response or nutrient intake and changes in modern lifestyles, with the widespread availability of nutritional supplementation, artificial lighting, and the like give rise to global patterns of disease, as well as other questions, arise from our currently limited understanding of host-virus interactions. Further research into seasonal immunological phenomena on a population level, especially with regard to influenza, is needed to bridge the gap between disciplines and allow seasonal immunology to be applied directly to the study and prevention of infectious disease.

PATHOGEN SURVIVAL AND TRANSMISSION: SOCIAL AND ENVIRONMENTAL CAUSES

When influenza virus occasionally makes the transition from its natural reservoir of wildfowl and spreads to humans, it is transmitted entirely through person-to-person contact. The viral particles replicate in respiratory epithelial cells and are subsequently excreted from the respiratory tract as small-particle aerosols (many less than 2 μm in size) during coughing, sneezing, or breathing. Incubation of the disease is very short, typically between 1 and 4 days. Spread from direct contact is also possible in some cases (35, 82), although theories of seasonality based on direct contact or large-droplet spread are not as well developed as those based on aerosol transmission. The classic susceptible-exposed-infected-recovered model of disease spread is extremely sensitive to the underlying population to which that model is being applied, as it provides both the pool of susceptible hosts who may come down with the disease and the already infected individuals (spreaders) who will pass the virus on to them. A model of influenza must, therefore, examine the behavior of the infected population and the possibility that the pattern of seasonal epidemics that characterizes flu is a result of the population itself.

Crowding. The person-to-person spread of virus-laden aerosol particles is greatly enhanced by having a dense population of susceptible individuals surrounding each infective subject, thereby maximizing the potential for the spread of infection. Crowding has therefore been implicated as a risk factor for a wide range of viral and bacterial diseases, including influenza (6, 11, 55, 64, 71). The origin and spread of the 1918 influenza pandemic has been attributed to the hypercrowded conditions on military bases during the First World War, allowing several theories concerning the pandemic's origin to emerge, one implicating the European Western Front (63) and another a U.S. Army base in otherwise-isolated and sparsely populated Haskell County, Kansas (8). The crowded conditions of the bases, as well as crude and undersupported medical facilities, would have given the otherwise-isolated flu outbreak a massive pool of susceptible individuals, who were then shipped all over the country and abroad to fight in the Great War, carrying the disease with them.

Given the profound effect crowding has on the spread of viral diseases and the emergence of epidemics, it is not surprising that it is often put forward as a potential source of seasonality. Seasonal fluctuations in host behavior might give influenza a greater opportunity to spread and maintain itself at epidemic levels during the winter (17). On a fundamental level, it is plausible that crowding and seasonal social/behavioral patterns are a source of seasonality, although no studies directly examining this causal relationship have been published. Much of the literature examining this theory treats crowding as a fundamental assumption from which to examine further, unrelated questions (30, 46, 66), and it is an especially frequent explanation of seasonality in the popular media. Only a few studies have directly examined this underlying assumption. Dowell (25), for example, addresses the plausibility of the theory critically, asking why—if crowding is the source of in-

fluenza seasonality—are there not frequent epidemics at busy international summer conventions? The answer might lie in crowding not being the driving cause of the seasonal incidence of influenza but a contributing factor, amplifying what would otherwise be a subtle and perhaps less-pronounced change in virus biology, transmission, or host response.

Ambient temperature. Decreased temperature is an environmental variable frequently found to be associated with high levels of seasonal influenza virus infection (20). Accepted as a basic assumption, this association has been used to explain the decreased effect of seasonality in the tropics (67) and is cited extensively—although not rigorously examined—in articles examining the incidence of acute respiratory infections (16, 21, 73, 75). No direct biological justification for this effect has emerged, and it is becoming an increasingly inadequate explanation as our view of seasonality is refined (26).

It may be that ambient temperature is simply extremely strongly correlated with the actual mechanism responsible for driving seasonality. These actual causes could be among those already discussed, such as a decrease in temperature inducing behavioral changes such as increased crowding. Or it may be another cause, as yet unexplored. Perhaps decreased ambient temperature increases physiological stress and energy costs for thermoregulation. These could, in turn, weaken the immune system, thereby increasing susceptibility to infection from an unaltered rate of exposure. Influenza in waterfowl is an enteric virus and has adapted to the higher temperature associated with fowl basal metabolism. The shift to a human host may have involved a cold-adaptation step that is further enhanced at colder temperatures. Another possible temperature-related factor is that viral particles are capable of prolonged persistence in colder environments. Given the unclear interactions among temperature, all of the myriad other correlated mechanisms proposed, and the biology of the influenza virus itself, further examination of this effect is clearly warranted.

Indoor heating. Paralleling the direct effects of temperature and harsh weather on the biology of either the host or the pathogen, human defenses against declining temperature may themselves contribute to the seasonality of influenza. Indoor heating levels should increase as the temperature drops, resulting in a continuously recirculated body of air with very low humidity. These conditions are ideal for the persistence of viral particles in the environment, with the typical furnace filter incapable of effectively filtering the very small particles to remove them from the circulating air, although this may be offset by inactivation of the virus at high temperatures. Lack of a concurrent increase in influenza virus infection in summer, when the use of air conditioning systems is high, may largely be the result of the mechanistic differences between the two systems. Air conditioning lowers the absolute humidity of the air via condensation (potentially trapping virus-bearing aerosols within the unit itself), while heating lowers only the relative humidity and never exposes the air to a wet condensing surface. Large-scale heating systems, such as those in apartment buildings, offices, and university dormitories would create a viral dispersion mechanism resembling the unintentional one potentially responsible for the Amoy Gardens severe acute respiratory syndrome outbreak (50). Thus far, this theory, though consistent with other hypotheses governing seasonality, has not been discussed in the literature or examined empirically in the case of influenza, although levels of indoor air pollution, which would be continually recirculated in the winter, have been shown to be risk factors for lower respiratory tract infections (70). Mathematical models have also been developed which examine the risk of indoor, airborne infection risks. Small changes in ventilation accounted for dramatic changes in the reproductive ratio (R_0; the number of secondary infections each primary infection gives rise to in an entirely susceptible population) for influenza virus, although the authors examined the risk of infection for single outbreaks and did not discuss mass ventilation changes such as those that may accompany the onset of winter as a potential driver of influenza seasonality (51).

Air travel. The role of air travel in the modern epidemiology of influenza has been examined in a substantial body of work, and its impact on the spread of the disease can be subdivided into two categories. The first is the role of air travel on the geographic spread of the disease after an epidemic or pandemic strain has emerged. Using data from the 1968 Hong Kong pandemic, models based on air traffic originating in Hong Kong and carrying passengers with an emerging strain of pandemic influenza virus show rapid and wide dissemination of the virus across both hemispheres (36). Beyond the model's implications for the spread of a major pandemic strain, the extremely rapid and universal spread of the hypothetical virus is also applicable to influenza seasonality. Flu season is characterized by the nearly simultaneous appearance of influenza epidemics hemisphere wide. Rapid dissemination of a virus via air travel provides a possible alternative to the theory that exposure is the result of a continually seeded viral pool. Such an alternative would have a substantial effect not only on the spread of a particular strain of the virus but in the global evolution of the disease and the host's immune responses. A constantly exposed population that becomes vulnerable to infection triggered by seasonal changes in virus biology, immunocompetence, or social habits is vastly different from a population which, due to the rapid flow of people and diseases across the globe, is periodically bombarded by new viral strains in a short period of time over a wide geographic area. The air travel dissemination model poses intriguing possibilities on the theoretical level, with the potential to shed light on the fundamental issue of the virus's passage through human populations. What is needed now is epidemiological and virological evidence to confirm (or fail to confirm) this particular mechanism of spread.

The second category of air travel studies show that it is possible to forecast the severity of the influenza season based on air traffic patterns. Using a standard compartmental model of influenza transmission coupled with data from U.S. air travel statistics, Grais et al. (36) were capable of predicting the influenza season of major U.S. cities and suggest that air travel has a role in the spread of influenza or in the creation of seasonal epidemics, as air travel has a large spike in the winter period, concurrent with the influenza season. The model's inability to accurately predict the incidence of influenza in several cities and the absence of a peak in influenza cases during the summer, a time of high air travel, are detailed by the authors (37).

Bulk aerosol transport. Beyond the issue of crowding, the aerosolization of influenza virus particles from infectious individuals may itself be directly responsible for the disease's seasonality. Coughing and sneezing (both symptoms of influenza) produce massive amounts of small-sized aerosol droplets with very high viral titers, which travel through the air at speeds of nearly 100 ft/s (77). A single patient or population of patients

could, over the course of several days, represent a significant source of aerosolized viral particles that could disperse over a wide area. Modeling of the 2003 severe acute respiratory syndrome outbreak at the Amoy Gardens housing complex in Hong Kong (which infected 329 people, killing 42) has very thoroughly examined the role of so-called "bioaerosols" in the transmission of disease (50). The nonuniform spatial pattern of the cases was found to be attributable to air currents created by the architecture and ventilation of the complex, which effectively circulated the virus particles produced by a single individual source to multiple apartments in the complex.

On a population level, an entire city experiencing an epidemic could produce staggering amounts of virus aerosols, yielding something not unlike the medieval concept of infective miasma. It has been suggested that this mass of infective particles is responsible for the seasonality of influenza by using global convective currents in much the same way as the ventilation system of the Amoy Gardens housing complex used air currents. Originating in Asia during the winter, aerosol particles may be conveyed into the upper atmosphere by frequently forming cyclogenic systems. Here, the low temperature and relative humidity of the upper atmosphere may enhance long-term survival of viral particles, allowing them to be picked up by a westerly air current and transported to North America within the span of a few weeks. Once over the North American continent, they are forced lower by frequent cold fronts. In the summer, the atmosphere over North America is less favorable to dispersion, and South Asian pressure systems are weaker and shift directions, severely depleting the flow of particles and, therefore, yielding the observed seasonal patterns of infection (39).

Although dispersed, the virus particles that survive this trip would find themselves in a favorable environment of cold temperatures and dry air both inside and out, both of which have been shown to be favorable for virus survival (42). Aerosolized transmission of influenza has been shown to be very efficient, and only a very small number of particles are needed to reach the lungs of a susceptible individual to initiate an epidemic (18). While the movement of small virus bioaerosols in the upper atmosphere is understandably difficult to measure, advances in the sampling of air for airborne viruses show promise for elucidating the quantity of influenza virus being carried on the wind (2, 3, 76). An expanded study of atmospheric patterns that would extend this mechanism to the rest of the world has yet to be brought forward and would have to be accompanied by actual sampling data to be useful in elucidating any possibility of seasonal fluctuations in the global spread of the virus. This notion of transoceanic movement of viruses in aerosolized form is extremely speculative and difficult to evaluate; however, several reported examples of transoceanic dust movements exist. Beyond the issues involved in the physical movement of the viral particles, the added issues of whether the virus can survive for such a long period of time and under increased exposure to UV radiation seem to make the likelihood of an infectious virus surviving a trans-Pacific journey somewhat unlikely.

El Niño. The El Niño Southern Oscillation (ENSO), a semiperiodic, long-term warming of the upper ocean in the tropical eastern Pacific Ocean, represents the largest signal of atmospheric-oceanic variation and is capable of influencing climates across the globe (80). Links between El Niño episodes and infectious disease have been widely reported for a number of different diseases. Oscillations in climate due to ENSO events were associated with influenza morbidity and mortality in France between 1971 and 2002, with a rise in both during cold periods of the ENSO cycle (79). A second study of the hospitalization of women in California for viral pneumonia between 1983 and 1998 showed a similar association for the city of Sacramento, CA, although it's results are much less clear and no association was found for San Francisco or Los Angeles (28). No biological mechanism for this association has been put forward, although it has been suggested that atmospheric and climatic variations caused by ENSO cycles may drive bulk aerosol transmission or increase crowding due to inclement weather.

MATHEMATICAL MODELING OF INFLUENZA

While many mathematical models have examined theoretical aspects of seasonality in host/pathogen systems, very few have tailored their investigations solely to the parameters and variables of influenza virus infection in humans. Although these more-abstract models are crucial to the understanding of infectious disease dynamics as a whole (including influenza), we will limit our discussion primarily to models which are strictly focused on the seasonality of influenza. Within this scope, theoretical models that have incorporated an examination of seasonal trends in disease incidence have chosen one of two main perspectives: seasonal forcing or emergent system properties.

Seasonal forcing, altering a model parameter at various points throughout the year, is the mathematical method of expressing an underlying process that affects the etiological rates of the disease based on a seasonal pattern in the occurrence of the process (52). This underlying process can stem from any source, and the motivations for including resulting changes in the parameters used to describe the disease dynamics can come either from a desire to incorporate mathematically some of the hypothesized theories governing seasonality already discussed (e.g., variations in host immunocompetence) or to prevent the absence of seasonal oscillation in the outcome from making it more difficult to validate model predictions using reported data. Mechanistically, seasonal forcing can be accomplished by altering parameters governing environmental exposure, the reproductive rate of the disease (R_0), or infectivity or by incorporating a separate variable into the model equations.

While seasonal forcing incorporates external, seasonally governed processes into mathematical models, it is possible to examine the internal mathematical properties of disease dynamics in order to look for inherent patterns of oscillation in the processes themselves. Closely related to the idea of true seasonal forcing is the idea of dynamical resonance (27). While models of seasonal forcing are founded on the belief that annual oscillations are driven by large-scale, observable changes, this theory proposes that many minute changes in R_0, so small as to be empirically undetectable, can act in concert with the duration of the infectious period and partial immunity, together generating regular seasonal oscillations. In general, these sorts of internally generated patterns are referred to as "emergent system properties" and can arise for a variety of different reasons. The most commonly studied is the phenomenon of bifurcation: the term used to describe systems that have a behavioral threshold beneath which they exhibit one set

of behaviors and above which they exhibit another. It has been shown many times in examining multiple strains of influenza in a model system that incorporates imperfect cross-protective immunity among strains that bifurcations can arise, yielding periodic oscillations (34, 61). A number of cross-protective immunity models, while not specifically examining bifurcation, have also incorporated rates of influenza virus strain mutation in order to produce seasonal trends (5, 68, 69).

Some models have tried to induce seasonality as an endogenous property of within-system dynamics, without altering either external seasonal forces or internal strain mutations or multistrain cross protection, based solely on theories of stochastic processes, the influence of random noise in the system, and cascading local effects (1). TRANSIMS (54) and EpiSims (29) are particularly ambitious in their attempts to capture all of the complexity of a functional society and experimentally examine the impact of direct intervention strategies on disease spread throughout a population. These models are now being adapted to directly examine the impact of pandemic influenza (7). One recent study (78) has examined the spatial movement of individuals on various scales as a factor in determining the synchrony of disease incidence across large distances. This spatial synchrony could then yield annual oscillations. These models attempt, each in its own way, to incorporate much of the complexity of real-life population dynamics and produce patterns of influenza incidence as emergent properties of populations themselves. Social interactions among different groups within a single population have also been shown to lead to oscillations in the incidence of influenza. By parameterizing the social interaction model presented by N. H. Fefferman and E. N. Naumova (unpublished data), using constant, age-specific values for the etiology of influenza taken from Longini et al. (53), we were able to produce incredible variation in the resulting influenza incidence patterns by comparing different interaction rates among social groups (Fig. 1). From these results, it is apparent that social interactions by themselves can be responsible for periodic oscillations. This lends mathematical support to the theory that many different facets must contribute to the resulting observed seasonal patterns and that, to understand the whole, it is important to understand all the components within a holistic context.

TOWARD A HOLISTIC VIEW OF SEASONALITY

The myriad theories accounting for seasonality reviewed in this paper, as well as those that will hopefully emerge as influenza continues to rise in prominence, suggest that the elegant and predictable periodicity of nonpandemic influenza is caused by a less-than-straightforward interaction of many different factors. The authors suggest that recognition of this complexity, as well as the likelihood that seasonality arises from many different factors, is essential for continued examination and elucidation of seasonality.

Of particular note are the gaps among theories and among disciplines. While epidemiologists, virologists, immunologists, and mathematicians have all developed laudable theoretical and empirical models to explain seasonality, none are so complete as to fully and adequately explain the phenomenon. Our decoding of the dynamics of nonpandemic influenza must take place on biological, social, and environmental levels, and, more

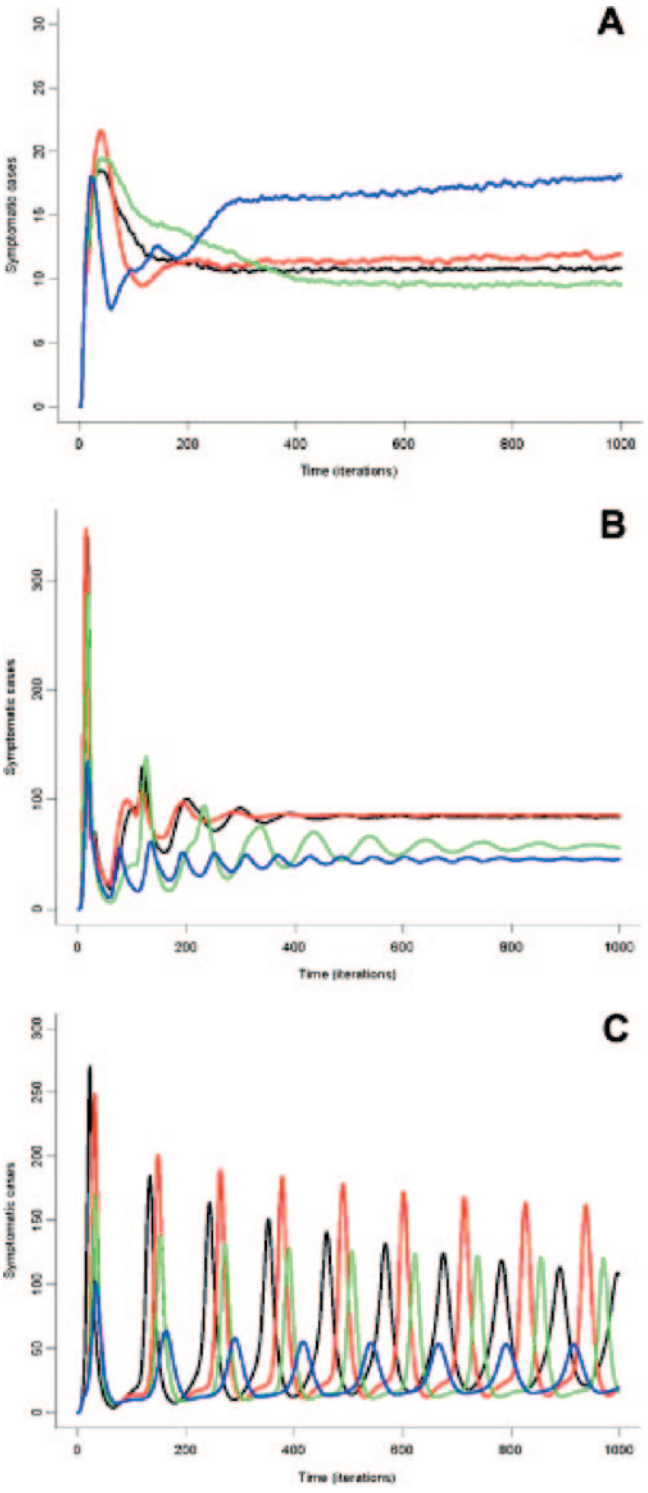

FIG. 1. Different patterns of influenza incidence in a total population, caused by different patterns of social interaction among four etiologically distinct age groups: children <5 years (black lines), children 6 to 20 years (red lines), adults (green lines), and the elderly (blue lines). All 12 modeled scenarios used the same population size and demography. The only differences among the modeled scenarios that yielded constant incidence of influenza (A), rapidly stabilizing, oscillating incidence of influenza (B), or long-term, periodic, oscillating incidence of influenza (C) were in the social interaction rates among these etiological groups. All parameter values and interaction rates held constant throughout each scenario.

importantly, must take place among disciplines. Complex networks of interactions among individual patients and their immune systems, society as a whole, global and local weather, and the continual mixing and adaptation of viral antigens to form new strains are likely responsible for seasonal flu infections and must be understood before steps can be taken in public health and medicine to positively affect health outcomes.

Influenza has been a constant global health concern since the pandemic of 1918, if not before, yet the most obvious trends in its incidence remain unexplained. Epidemiological investigations have primarily incorporated seasonality as an underlying assumption, focusing on other aspects of flu transmission and exposure. As previously discussed, the proposed theories explaining the causes of seasonal trends in flu incidence span many facets of epidemiology, ranging from specific genetic properties of the virus, to the buildup of pollution in indoor heating systems, to the paths of global wind streams. Alternatively, the answer may be as yet unconsidered. It is our intention that this paper provides a framework from which further empirical and theoretical investigations specifically into the causes of seasonality in influenza may be undertaken. Studies seeking novel mechanisms and those providing both biological plausibility and epidemiological evidence for existing theories are needed. An understanding of what drives seasonal trends may allow better understanding of transmission dynamics, leading to better methods of prevention of annual endemic outbreaks, of pandemics of already existing flu strains, and of novel emerging influenza strains.

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